

Prenatal Study of Fetal Endocardial Hyperrefringence and its Relation to Maternal Toxoplasmosis

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Objective - To compare a group of fetuses whose mothers had acute or recent toxoplasmosis with a group of fetuses whose mothers had no systemic disease, analyzing the presence of changes in endocardial refringence.

Methods - This study assessed 91 fetuses of mothers diagnosed with acute or recent toxoplasmosis, detected by seroconversion or the presence of elevated IgM and IgG titers, confirmed through the IgM-capture ELISA. They were compared with a control group comprising 182 fetuses selected from a low-risk population participating in a prenatal screening program for heart diseases.

Results - No significant difference was observed between the mean gestational (29.2 ± 4.6 weeks; 29.2 ± 4.6 weeks) and maternal (25.7 ± 6.7 years; 26 ± 5.4 years) ages in the 2 groups. Areas of endocardial hyperechogenicity were observed in 69 fetuses whose mothers had toxoplasmosis (75.8%) and in only 6 fetuses of the control group (3.3%) ($P < 0.001$). In 52 patients of the group studied (75.4%), endocardial hyperrefringence was diffuse, and, in 17 (24.3%), it was focal. In the control group, focal distribution was observed in 5 fetuses (83.3%).

Conclusion - The prenatal echocardiographic image of focal or diffuse endocardial hyperrefringence is more prevalent in pregnancies with maternal toxoplasmosis than in the healthy ones, and an association between fetal endocardial hyperechogenicity and maternal disease exists.

Key words: fetal heart, congenital toxoplasmosis, endocardial fibroelastosis, imaging diagnosis

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Transmission of maternal toxoplasmosis to the fetus, as well as the risk and severity of the fetal disease, varies according to the gestational age at which the maternal infection is acquired¹⁻⁴.

Until the present time, no specific criterion is known for the in vivo diagnosis of fetal cardiac impairment by *Toxoplasma gondii*, except for the functional changes⁵⁻⁸. This study assesses the possibility of the fetal echocardiogram showing occasional abnormalities consequent to toxoplasmosis.

Echogenic intracardiac foci, or golf balls, are small hyperechoic areas with echogenicity very similar to that of bone structures, usually located close to the papillary muscle and chordae tendineae⁹⁻¹². We observed that 0.17% to 20% of the fetuses between the 15th and 22nd gestational weeks undergo ultrasonography^{10,13-15}.

In the prenatal screening for congenital heart diseases, the occasional finding of intracardiac golf balls is considered, by many authors, a normal variant of the development of the papillary muscles of the mitral valve or of the chordae tendineae^{14,16}. On the other hand, other authors have shown that the presence of these fetal heart findings may suggest the diagnosis of changes, such as cardiac tumors, myocardial dysfunction, or congenital structural heart disease^{13,17}. In addition, some researchers have referred to them as possible ultrasonographic markers of fetal aneuploidy^{10,13-15,17-24}.

Obstetrical ultrasonography may be used to assess fetal and neonatal infections²⁵. Several studies exist in the literature associating the presence of areas of calcification in the brain, heart, and liver of neonates with infections, possibly acquired in utero, such as toxoplasmosis and herpes simplex^{7,26-28}.

Preliminary observations at the Unit of Fetal Cardiology of the Institute of Cardiology of Rio Grande do Sul have shown the presence of focal or diffuse endocardial hyperrefringence in fetuses referred for fetal echocardiography due to maternal toxoplasmosis different from the classic golf balls previously described²⁹. That is why the hypothesis that fetal endocardial echogenicity may be related to maternal toxoplasmosis was formulated.

Methods

A controlled cross-sectional study was carried out in a population composed of pregnant women with gestational ages ranging from 20 weeks to term, referred by obstetrical services in the city of Porto Alegre to participate in the fetal echocardiographic program for screening of heart diseases at the Fetal Cardiology Unit of the Institute of Cardiology of Rio Grande do Sul from December 1999 to December 2001.

Fetuses with the following characteristics were excluded from the study: gestational age lower than 20 weeks; structural or chromosomal abnormalities; retardation of intrauterine growth; mothers with other associated diseases (diabetes mellitus, systemic arterial hypertension, infections, collagenoses, etc); and technically inadequate visualization of the fetal heart due to fetal position, oligohydramnios, or maternal obesity.

The diagnostic criteria for acute or recent maternal infection by *Toxoplasma gondii* were based on the serum titers of IgM and IgG antibodies to *Toxoplasma* obtained with the Microparticle Enzyme Immunoassay-MEIA (AXSYM) method, which, when reacting, were confirmed by the IgM-capture ELISA. The definitive diagnosis was established when maternal seroconversion could be detected.

The sample comprised 110 pregnant women diagnosed with acute or recent toxoplasmosis from the Outpatient Care Clinics of High-Risk Obstetrical Pathology of the Hospital Nossa Senhora da Conceição referred for fetal heart screening in our service. Nineteen patients did not meet the inclusion criteria for the project because of systemic diseases or fetal abnormalities. Therefore, the study comprised 91 pregnant women diagnosed with toxoplasmosis, who were sequentially and randomly selected, independent of the serum titers at the time of fetal echocardiography, because the patients had their diagnoses confirmed at the referral center, even when their titers were negative or in regression.

The control group was randomly and sequentially selected, comprising 182 healthy fetuses strictly paired for gestational age, whose mothers were healthy with normal serum titers for acute or recent toxoplasmosis.

The observer performed the fetal echocardiograms with no previous knowledge about the maternal status concerning toxoplasmosis.

The fetal heart was analyzed in the classical manner previously described³⁰, following a segmentary sequential approach using M mode, 2-dimensional imaging, and Doppler color flow mapping. The cardiac structures were assessed in 4-chamber, longitudinal, cross-sectional, and sagittal views using the Acuson XP-10 and Aspen devices with sectorial or convex 4.0-, 5.0- or 7.0-mHz transducers.

Once structural or other abnormalities were ruled out, 2-dimensional echocardiography was performed to analyze the presence of intracardiac hyperechogenic foci or areas of increased echogenicity in the mitral and tricuspid valvular and subvalvular apparatus, as well as on the endocardial septal surface and in the ventricular wall. Aiming at minimizing possible measurement biases, the gain was strictly observed during the examination, being reduced whenever necessary (figs. 1 and 2).

Mean and standard deviation were used for the description of quantitative variables, and the absolute and relative

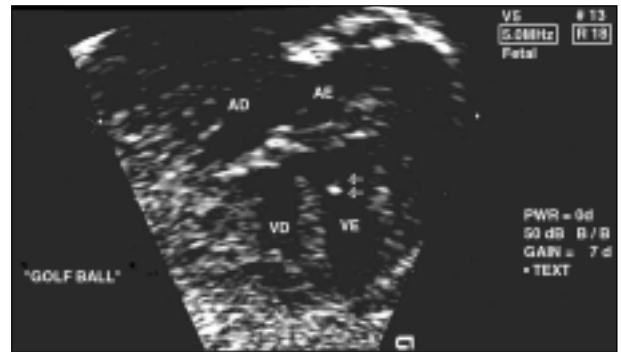


Fig. 1 - A 29-week-old fetus with focal hyperechoic image (golf ball) close to the mitral subvalvular apparatus (control group).



Fig. 2 - Areas of diffuse hyperrefringence affecting the mitral subvalvular apparatus and the left ventricular endocardial surface of the septum in a 34-week-old fetus, whose mother had acute toxoplasmosis.

frequencies were used for qualitative variables. The comparison of the maternal and gestational ages between the groups was performed using the Student *t* test. The remaining variables were compared using the Pearson chi-square test and Fisher exact test, when necessary, and their magnitudes were described based on odds ratio with a 95% confidence interval. The significance level adopted was 0.05.

Results

The mean age of the pregnant women with toxoplasmosis was 25.7 ± 6.7 years, and that of those in the control group was 26 ± 5.4 years ($P=0.69$). The mean gestational age of the women with toxoplasmosis was 29.2 ± 4.6 weeks, and that of the controls was 29.2 ± 4.6 weeks ($P=1.00$). Table I shows that no significant difference was observed between the maternal and gestational ages when comparing the fetuses with and without endocardial hyperrefringence.

Figure 3 shows that 69/91 (75.8%) fetuses whose mothers had toxoplasmosis had endocardial hyperechogenicity, while only 6/182 (3.3%) control fetuses had that finding.

Figure 4 shows that 52/69 (75.4%) fetuses whose mothers had toxoplasmosis had diffuse hyperrefringence, while 5/6 (83.3%) control fetuses had focal hyperechogenicity. This difference was significant ($P<0.007$), with an odds ratio of 15.29 (CI= 1.66 – 140.22) (fig. 4).

Figures 5, 6, and 7 show the relative frequencies of the diverse locations of focal and diffuse endocardial hyperechogenicity. In the group with maternal toxoplasmosis, both

focal and diffuse hyperrefringence were mainly located in the mitral subvalvular apparatus, 64.7% and 71.2%, respectively. In the control group, 3/5 (60%) fetuses showed hyperrefringence in the same location, the mitral subvalvular apparatus. The only control with diffuse hyperrefringence had it in the mitral valve.

Discussion

The screening for congenital toxoplasmosis is associated with diagnostic difficulties inherent in the gestational age

	Presence	Absence	Difference (95% CI)	P
Maternal age	25.6 ± 6.7	26 ± 5.5	-0.38(-2.1;1.3)	0.66
Gestational age	28.8 ± 4.7	29.3 ± 4.6	-0.48(-1.7;0.7)	0.44

Student *t* test.

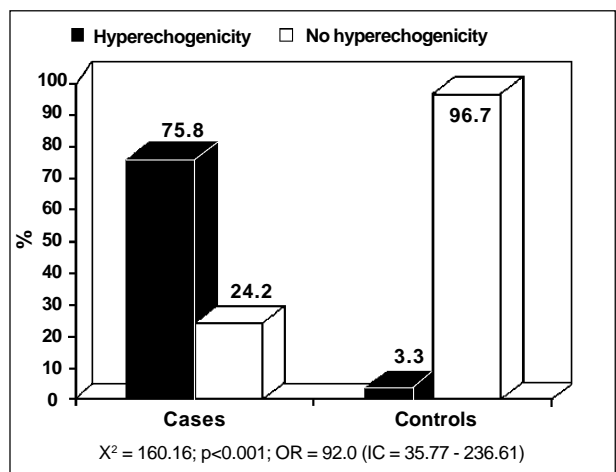


Fig. 3 - Endocardial hyperrefringence in the fetuses whose mothers had toxoplasmosis and in the controls.

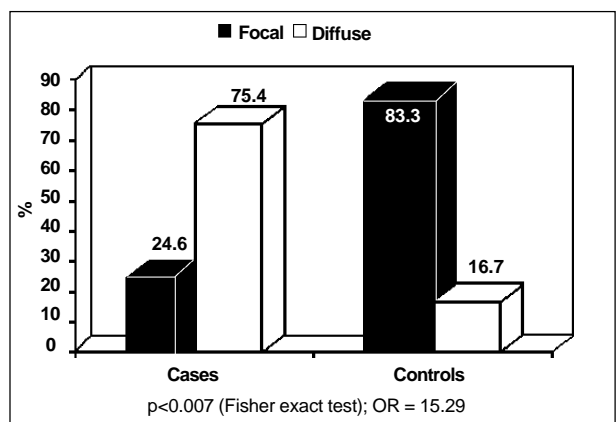


Fig. 4 - Extension of endocardial hyperrefringence in the fetuses whose mothers had toxoplasmosis (n=69) and in controls (n=6).

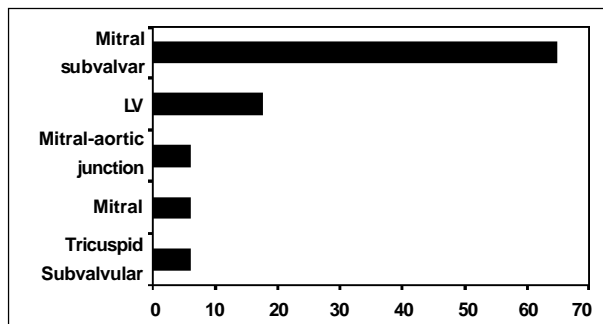


Fig. 5 - Relative frequency of the locations of focal hyperrefringence in the fetuses whose mothers had toxoplasmosis.

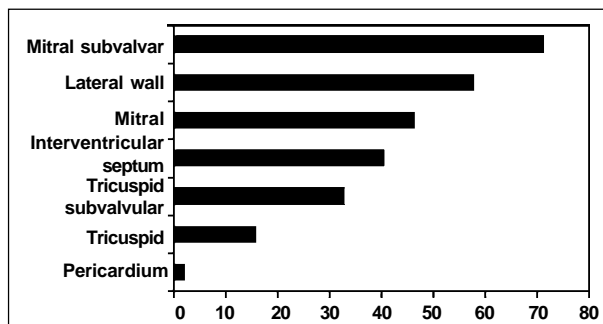


Fig. 6 - Relative frequency of the locations of diffuse hyperrefringence in the fetuses whose mothers had toxoplasmosis.

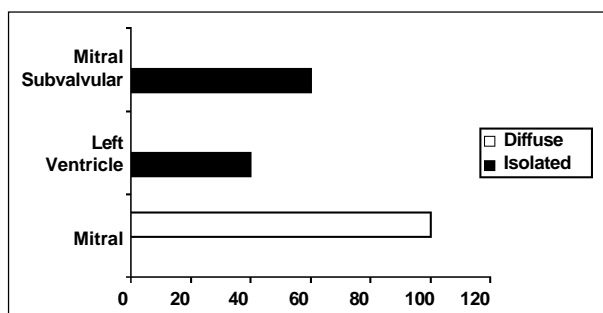


Fig. 7 - Relative frequency of the locations of hyperchoic foci in the controls.

at which maternal infection occurs, because only rarely is the maternal immunologic status known prior to conception and also because the serum measurements prior to conception are frequently performed at different laboratories and cannot be compared^{31,32}. In addition, approximately 90% of the patients with acute infection are asymptomatic^{31,33}, and, most of the time, no evident clinical suspicion exists, making the diagnosis dependent on laboratory assessment.

The relation between the presence of hyperrefringent areas and serum titers of antibodies was not performed, because the pregnant women underwent echocardiography at different stages of their disease evolution.

In the literature, reports can be found about the association of the presence of extracardiac calcifications with echographic signals of fetal toxoplasmosis^{34,35}. Many authors have reported that hyperechoic areas in the brain, liver, intes-

tine, and pericardium may signify a possible fetal infection. In addition, some cardiac abnormalities have been related to infection by *Toxoplasma gondii*, both in children and adults, with no description of fetal cardiac impairment^{1,5-8}.

This study found a very high frequency of areas of diffuse hyperrefringence in the endocardium and in the subvalvular apparatus of the heart of fetuses whose mothers had a serum diagnosis of toxoplasmosis, independent of the fetus being infected or not. Since the beginning of our observations, attention has been given to the fact that these findings disagree with those previously reported by Schechter et al in 1987¹², because they were diffuse, frequently affecting the endocardial septal surface and both atrioventricular valves.

Based on these differences, the possibility that these alterations might be an ultrasonographic marker for toxoplasmosis was raised. Later observations of these findings also in fetuses of mothers with other infections, such as rubella, AIDS, influenza, and cytomegalovirus infection, have suggested the possibility that these findings may be occasional nonspecific markers for several infections, and not necessarily only for toxoplasmosis.

In 75.8% of the fetuses of mothers diagnosed with acute or recent toxoplasmosis, endocardial hyperrefringent areas were identified, while in fetuses of mothers without the disease, only 3.3% had that alteration, suggesting that the presence of these findings could be associated with infection.

Diffuse hyperechogenic areas were found in 75.4% of the fetuses of mothers diagnosed with toxoplasmosis, while in the group of mothers without the disease, the focal form was evidenced in 83.3%. In the latter group, the findings agreed with those in the literature, and referred to the presence of isolated intracardiac echogenic foci, whose prevalence of 3.3% was very similar to that reported by some authors^{10,13-15,36}.

It is worth emphasizing that the visualization of areas of diffuse hyperechogenicity in the heart of fetuses of mothers with toxoplasmosis with hyperechoic areas distributed in a wide endocardial area, or in the valvular and subvalvular apparatus, or both, is different from the focal images

classically referred to as golf balls, which are roundish structures, with well-demarcated borders, visualized according to the fetal position.

In the fetuses of mothers with toxoplasmosis, the relative frequency of the preferential localization of the focal hyperechogenicity was greater in the mitral subvalvular apparatus (64.7%) and in the left ventricle (17.6%), very similar to that of the echogenic foci found in the general population. On the other hand, in the control group, the distribution of the isolated images did not differ from that of the intracardiac echogenic foci reported in the literature.

As with the isolated impairment, these findings have no definitive explanation, but the endocardial mineralization areas similar to those described in other organs, consequent to the infection by *Toxoplasma gondii*, may occur in the fetal heart in an analogous manner. As already mentioned, similar images have also been described in other infections, emphasizing the idea that these findings are not specific.

This study raises some questions that may be the object of other research projects. Therefore, the histological bases of the hyperechogenic images of the fetal heart need to be clarified, as does the association of their presence with PCR for toxoplasmosis in the amniotic fluid. In addition, the role played by acute or recent toxoplasmosis on maternal endocardium during gestation and puerperium remains unknown, as does the postnatal evolution of fetal hyperechogenic images. Finally, the hypothesis that the diffuse fetal endocardial hyperrefringence may be accompanied by alterations in ventricular complacence or relaxation has not yet been tested.

In conclusion, based on the comparative study of data obtained from a sample of fetuses whose mothers had acute or recent toxoplasmosis and those of a control group constituted of fetuses whose mothers had no infection, the prenatal echocardiographic image of focal or diffuse fetal endocardial hyperrefringence is more prevalent in gestations with maternal toxoplasmosis than in normal gestations. An association exists between the presence of fetal endocardial hyperechogenicity and maternal toxoplasmosis.

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